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Nucleoside Analogs

Nucleoside analogs were among the first compounds shown to be effective against viral infections. The pioneering work of Elion and colleagues at Burroughs-Wellcome led to the development of acyclovir which is used extensively in the treatment of herpetic infections (1). Therefore, it is not surprising that the first four anti-HIV drugs to be approved, AZT, ddI, ddC and D4T ; were nucleoside analogs. All four of these drugs and other nucleoside analogs are believed to have a similar mechanism of HIV inhibition, in which the nucleosides are progressively phosphorylated to a 5'-triphosphate, which then acts as a chain terminator in a reverse transcriptase (RT) reaction.

Anti-HIV activity is dependent on the intracellular phosphorylation of the analog and the ability of the phosphorylated analog to interact with the HIV-RT. The rate limiting step in most cells is believed to be the initial phosphorylation by nucleoside kinases, or in the case of AZT, the conversion of a nucleoside monophosphate to a nucleoside diphosphate. Many 2'-3' dideoxynucleoside analogs have potent inhibitory effects on viral RT when in the triphosphate form, but little effect as a nucleoside on HIV infected cells. This lack of activity is believed to be due to low affinity between the nucleoside or nucleotide analog and cellular kinases, such as thymidine kinase. Nucleoside kinase and nucleotide kinase activity varies widely between cells. Some HIV-infectable cells, such as monocytes and macrophages, when at rest, are believed to have little kinase activity. This could account for the inability of AZT and other nucleoside analogs to prevent transmission when given immediately after HIV exposure. Prodrugs such as methoxyglycinyl derivatives and bis[S-(2-hydroxyethylsulfidyl)-2-thioethyl] esters have been designed to form monophosphorylated nucleoside analogs intracellularly. Acyclic nucleoside phosphonates, such as 9-(2-phosphonylmethoxyethyl)adenine (PMEA), have also been used to overcome the kinase bottleneck. The acyclic phosphonate analog, 9-(2-phosphonylmethoxypropyl)adenine (PMPA) has been reported to prevent SIV transmission in macaques, even when administered 24 hours after exposure (2).

Another approach to increase the potency of nucleoside analogs has been to use potentiating drugs to increase the amount of dideoxynucleoside triphosphates and decrease the amount of deoxynucleoside triphosphates. Ribavirin and hydroxyurea have been shown to enhance the anti-HIV activity of ddI by suppressing the formation of dATP and facilitating the conversion of ddI to ddATP without increasing the toxicity of ddI.

The major limitations of nucleoside analogs include their toxicity, lack of activity in some cell types, and susceptibility to viral resistance. Toxic side effects vary from compound to compound: anemia and/or neutropenia are frequently seen with AZT; neutropenia and

peripheral neuropathy with 3TC; peripheral neuropathy with ddC , D4T and ddI; and acute pancreatitis with ddI. HIV viral isolates from patients are often resistant to the nucleoside analog that was used therapeutically in the patient. Resistance has also been reported in patients who have not been treated with nucleoside analogs.

The mutations responsible for viral resistance to nucleoside analogs have all been mapped to the RT enzyme. The five following mutations in HIV-1 RT, confer a high level of resistance to AZT: 41 Met--Leu; 67 Asp--Asn; 70 Lys--Arg; 215 Thr--Phe/Tyr; 219 Lys--Gln. Multiple mutations in RT have also been reported to occur in an ordered fashion, such as: 41--41/215--41/67/215--41/67/70/215--41/67/70/215/219; with each mutation leading to accrued resistance. Although extensive structural and genetic studies have been done on AZT resistant enzymes, a biochemical explanation for AZT resistance is still lacking. Most AZT-resistant enzymes bind AZT-triphosphate with the same avidity as nonresistant enzymes. Resistance to ddI is conferred by the 74 Leu--Val mutation, the 69 Thr--Asp mutation reduces susceptibility to ddC ; the 75 Val--Thr mutation confers resistance to D4T . The 184 Met--Val mutation not only confers multiple resistance to ddC , 3TC and ddI, but also will supress the effects of AZT resistant mutations resulting in an enzyme that is once again susceptible to AZT. Enzymes containing the 184 Met--Val mutation also makes 50-fold less errors compared to the wild-type enzyme. This increased fidelity that results from 3TC resistance, should also reduce the appearance of protease resistant strains. Currently, many treatment regimens consist of two nucleoside analogs (i.e. AZT and 3TC), and a protease inhibitor. These treatments are designed to lead to the greatest reduction in viral burden and also to prevent protease resistant strains from appearing (3).

Nucleoside analogs will continue to play a major role in anti-HIV therapy, current efforts are underway to develop analogs that are less toxic, less susceptible to viral resistance and less dependent on kinases whose activity varies from cell to cell. Nucleoside analogs less susceptible to resistance and effective in a wider variety of cells could play a major role in achieving HIV viral eradication and in preventing initial HIV infection.

Approved Nucleoside Analogs

- AZT
- 3TC
- ddI
- ddC
- D4T
- Abacavir Succinate

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HIV drug summary

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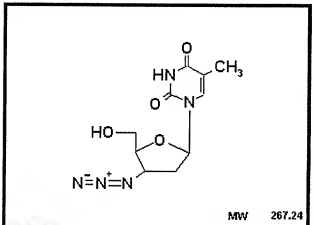
Zidovudine; AZT; Azidothymidine; Retrovir® ZDV



NAME	3'-Azido-3'-deoxythymidine
SYN	AZT; Azidothymidine; Zidovudine; Retrovir; ZDV
COMP	GLAXO WELLCOME

AZT was one of the first nucleoside analogs shown to have potent anti-HIV activity in-vitro (1). AZT enters cells by passive diffusion, and appears to be phosphorylated by the same enzymes that convert thymidine (dT) to dT-5'-TP. AZT-triphosphate (AZT-TP) is the active species, acting as a chain terminating substrate for HIV reverse transcriptase (HIV-RT) during either first or second strand DNA synthesis. Although resistance to AZT frequently develops, the addition of 3TC (Lamivudine) to a therapeutic regimen can cause AZT-resistant strains to revert to AZT-sensitive strains (4).

In-vitro Data

Cell	Strain	EC50^	IC50^^	Units	TI^^^	Reference
PBMC (PHA STIM.)	HIV-1(IIIB)	0.05	>50	µM	>1000	1
ATH8	HIV-1(IIIB)	1-5	>10	µM	>10	1
MT4	HIV-1(IIIB)	0.006	4	µM	667	2
PBL(PHA	HIV-1(IIIB)	0.09	14*	µM	156	3

STIM.)						
PBL(PHA STIM.)	HIV-1(CLINICAL ISOLATES (MEAN OF 54))	0.23	0.3**	µM	1.3	3
HeLa CD4+	HIV-1(HXB2-D)	0.01	-	µM	-	4
HeLa CD4+	HIV-1(HIVRTMN (RT-M41L,T215Y))+	0.7	-	µM	-	4
HeLa CD4+	HIV-1(HIVRTMN P9(RT-M41L,T215Y))++	1.36	-	µM	-	4
HeLa CD4+	HIV-1(HIVRTMN P10(RT-M41L,T215Y, M184V))#	0.01	-	µM	-	4

^EC50 (also commonly referred to as ED50 or IC50) is the effective concentration that inhibits 50% of viral production, 50% of viral infectivity, or 50% of the virus-induced cytopathic effect.
^^IC50 (also referred to as CC50, CD50; TC50,TD50 or cytotoxicity) is the inhibitory concentration that reduces cellular growth or viability of uninfected cells by 50%.
^^^TI (also known as SI or selectivity index) is the therapeutic index which is equal to IC50/EC50.
*IC50=% Inhibition granulocyte.-macrophage colony formation of human bone marrow progenitor cells
**IC50=% Inhibition erythroid blast forming units of human bone marrow progenitor cells
+AZT resistant strain
++AZT resistant strain passaged 9X in 5 µM AZT and increasing conc.entrations of 3TC (Final conc.=50 µM).
#AZT resistant strain passaged 10X IN 5µM AZT and increasing concentrations of 3TC (Final conc.=100 µM); M184V mutation is also seen in most patients after six weeks of AZT/3TC combination therapy and is associated with the conversion of an AZT resistant strain to an AZT sensitive strain.

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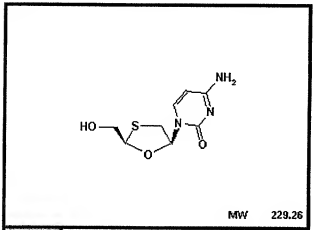
Lamivudine; 3TC; Epivir®



MW 229.26

NAME	cis-1-[2'-Hydroxymethyl-5'-(1,3-oxathiolanyl)] cytosine
SYN	(-)-BCH-189; DTHC; 3TC; Lamivudine; Epivir; L-(-)-S-ddC
COMP	IAF BIOCHEM INT/GLAXO WELLCOME

In-vitro Data

Cell	Strain	EC50	IC50	Units	TI	Reference
CEM	HIV-1(RF)	0.18	>363	µM	>2016	1
CEM	HIV-2(ROD)	0.24	>363	µM	>1512	1
PBMC	HIV-1(LAI)	0.07	-	µM	-	2
PBMC	HIV-1(LAI, RT-M184V, 3TC RESISTANT)	>100	-	µM	-	2

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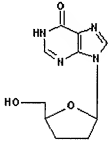
Didanosine; Videx®; Dideoxyinosine; ddI



MW 236.23

NAME	2',3'-Dideoxyinosine
SYN	DDI; D2I; ddIno; Didanosine; Videx
COMP	BRISTOL-MYERS SQUIBB

In-vitro Data

Cell	Strain	EC50	IC50	Units	TI	Reference
ATH8	HIV-1(IIIB)	8	1000	µM	125	1
MT-4	HIV-1(IIIB)	10	>500	µM	>50	2
PBMC	HIV-1(LAV)	0.46	>100	µM	>217	3

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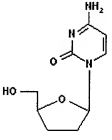
Zalcitabine; Hivid®; Dideoxycytosine; ddC



MW 211.22

NAME	2',3'-Dideoxycytidine
SYN	ddC; ddCyd; D2C; Zalcitabine; Hivid
COMP	HOFFMAN- LA ROCHE

In-vitro Data

Cell	Strain	EC50	IC50	Units	TI	Reference
ATH8	HIV-1(IIIB)	0.3	30	µM	100	1
MT-4	HIV-1(LAV)	0.046	9.1	µM	198	2
PBMC(PHA STIM.)	HIV-1(LAV)	0.011	>100	µM	>9091	2

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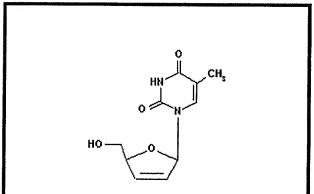
Stavudine; Zerit®; D4T



MW

NAME	Thymidine, 2',3'-didehydro-,3'-deoxy-
SYN	D4T; ddeThd; ddeTyd; DHT; Stavudine; Zerit
COMP	BRISTOL-MYERS SQUIBB

In-vitro Data

Cell	Strain	EC50	IC50	Units	TI	Reference
PBMC	HIV-1(LAV)	0.0088	-	µM	-	1
MT-4	HIV-1(IIIB)	0.05	19	µM	380	2
PBMC(PHA STIM.)	HIV-1(LAV)	0.009	70	µM	7777	3

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HIV drug summary

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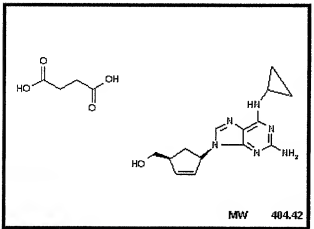
Abacavir; 1592U89 succinate; Ziagen



MW 404.42

NAME	Butanedioic acid, compd. with (1S-cis)-4-[2-amino-6-(cyclopropylamino)-9H-purine-9-yl]-2-cyclopentene-1-methanol (1:1)
SYN	Abacavir ; 1592U89 succinate; Ziagen
COMP	GLAXO WELLCOME

Abacavir is a carbocyclic nucleoside analog which is activated intracellularly to (-)-carbovir triphosphate by a unique mechanism (6). It is first phosphorylated to abacavir monophosphate, then deaminated to (-)-carbovir monophosphate and finally phosphorylated to (-)-carbovir triphosphate (CBV-TP). The enzyme responsible for deamination is not adenosine deaminase or adenylic acid deaminase but a novel enzyme that appears to have wide tissue distribution. CBV-TP is incorporated by HIV reverse transcriptase into proviral DNA resulting in chain termination. Abacavir has shown good bioavailability (92% in mice, 77% in monkeys) and penetrates into the monkey cerebral-spinal fluid and the mouse brain to a similar extent as AZT. Abacavir is significantly less toxic to the hemopoietic system than AZT (1, 4). Abacavir appears to be synergistic in anti-HIV activity in combination with AZT, ddI or ddC. In in-vitro studies resistance developed slowly and strains were cross-resistant to ddI and ddC. The RT-M184V mutation, a mutation associated with increased sensitivity to AZT in AZT-resistant strains, was the first mutant seen upon passage (2,5). As a monotherapy, in clinical studies, abacavir appears to have a stronger anti-HIV effect than any of the approved nucleoside analogs. A dose-ranging study reported a greater than 1.4 log reduction in HIV RNA plasma levels after four weeks of abacavir monotherapy at all doses tested (3).

In-vitro Data

Cell	Strain	EC50	IC50	Units	TI	Reference
PBL	HIV-1(Clinical Isolates)	0.26	100 (BFU-E)*	µM	385	1, 4
PBL	HIV-1(IIIB)	4	-	µM	-	2, 4
MT-4	HIV-1(IIIB)	4	-	µM	-	2, 4
HeLa CD4+ HT4-6C	HIV-1(HXB2)	6.5	-	µM	-	2, 4
HeLa CD4+ HT4-6C	HIV-1 (HXB2 (RT-M184V,K65R,L74V))	65	-	µM	-	2, 5

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